23. The composition of claim 15 wherein said surfactant further comprises two surfactants, one of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil and the second of which is a polyoxyethylene-sorbitan-fatty acid ester.

REMARKS

The Examiner has rejected Claim 19 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant therefore has amended claims 18 and 19, and provided new claims 22 and 23 to overcome the Examiner's rejections. Full reconsideration is requested.

The Examiner has rejected Claims 15, 17 to 19 under 35 U.S.C. 102(e) as being anticipated by Hong et al (U.S. Patent No. 6,063,762). The Examiner is advised that Hong et al is not a bona fides reference in that the priority filing date of Applicant's application (April 29, 1997) predates the priority filed date of Hong (December 5, 1997). Therefore Hong would not have been available to those skilled in the art on Applicant's priority filing date and Hong therefore must be withdrawn as prior art.

Applicant hereby request that the Final Rejection issued in the prosecution of this Application be withdrawn pursuant to M.P.E.P 706.07 (c) and (d) as it was premature to issue the said Final Action in view of the fact that the primary reference cited as prior art against Applicant's claims, namely Hong, et al (U.S. Patent No. 6,063,762) is not bona fides prior art in that Applicant's priority filing date of April 29, 1997 predates the Foreign Application Priority Data (Rep. of Korea, 97-66454) for Hong, et al of December 5, 1997. It is therefore requested that the holding of the Examiner's action of March 28, 2002 as being FINAL be reconsidered and withdrawn. Further in view of the fact that Hong is not prior art the Examiner's above-mentioned anticipation rejection is moot and should be withdrawn. Full reconsideration is requested.

The Examiner has rejected Claims 1 to 21 under 35 U.S.C. 103(a) as being unpatentable over Woo (U.S. Patent No. 5,589,455) or Kim et al (U.S. Patent No. 5,980,939), in view of Hong et al (U.S. Patent No. 6,063,762).

As discussed above Hong should be withdrawn as prior art and therefore the teachings thereof would not be available to combine with Woo or Kim. Fundamentally therefore the Examiner's alleged obviousness rejection set out on page 4 and 5 of her report is also moot since the teaching of Hong was not available to Woo or Kim on the filing date of Applicant's priority New Zealand application . How then could Woo or Kim be motivated to substitute their oil component with that of Hong if the teachings of Hong; both U.S. Patents No. 6,063,762 and 6,028,067; were not available to them on the filing date of Applicant's priority application of April 29, 1997. Both Hong et al patents have the same priority filing date of December 5, 1997.

Referring now to United States Patent No. 5,980,939 to Kim hereinafter referred to as Kim as with the case of Woo there is taught at column 5, line 5 onward a pharmaceutical composition including cyclosporin, propylene carbonate or various mixtures thereof as stated, as a hydrophilic solvent, an oil component (mixtures of mono and di-glycerides (see column 8 line 8) and a surfactant. There is no discussion within the Kim reference with regard to the advantages of using only acetylated monoglycerides. This distinction is discussed at page 3 at the bottom thereof in Applicant's disclosure discussing the prior art mixing of the various mono- and di-glycerides. In relation to page 7 of Applicant's teaching, there is set out the advantage of acetylated monoglycerides as being low cost and that they are effective good solvents for cyclosporins reducing the amount of lipophilic solvent required and/or reducing the need for a hydrophilic co-solvent. If required the acetylated monoglycerides are readily intradissolved with preferred hydrophilic co-solvents, and finally that they become readily dispersible into emulsions or microemulsions upon inclusion of a suitable surfactant. Therefore acceptable emulsion preconcentrates or micro-emulsion preconcentrates can be made using

only cyclosporin, acetylated monoglycerides and a surfactant. This limitation is set out in amended Claim 1 as set out below.

Clearly, there is no teaching within Kim to provide such an emulsion preconcentrate. There is no motivation within Kim to provide a emulsion preconcentrate with the further limitation of the emulsion preconcentrate including fully acetylated mono-glycerides, and not combinations of mono-glycerdies, di-glycerides and tri-glycerides as per the teachings of Kim and or Woo. There is no teaching in Kim and for that matter neither in Woo relating to the advantages of using fully acetylated monoglycerides as per the teachings of Applicant. Kim teaches various permutations and combinations which respectively do not focus in on Applicant's invention. Further, referring to the claims of Kim, clearly the invention is specified as including either a medium chain triglyceride or a mixture of monoglycerides, diglycerides and triglycerides. Kim therefore is silent in relation to Applicant's invention as set out in the amended claims set out herein.

Referring to United States Patent No. 5,589,455 to Woo, hereinafter referred to as Woo there is taught a micro-emulsion concentrate containing cyclosporine as the active with no discussion whatsoever of utilizing acetylated monoglycerides as liquifilic solvent for cyclosporine. The Woo reference teaches in fact, micro-emulsion concentrate containing cyclosporine in combination with a carrier consisting of a hydrophilic high molecular weight solvent, specifically polyethylene glycol or dimethylisosorbide, as a co-surfactant and an oil component such as fish oil or a mixture of medium chain fatty acid triglycerides and fatty acid monoglycerides as the oil component, and a surfactant, which is suitable for formulation into soft capsules for oral administration. Refined fish oil is defined as being ideally fit for the absorption of cyclosporin since it contains a highly saturated fatty acid, such as EPA and DHA. This is not part of Applicant's teachings and in fact, Applicant is using unsaturated acetylated mono-glycerides which is not a mixture of fatty acids. Further, there is no teaching in Woo of the advantages of utilizing within the micro-emulsion, small droplets and just how small those droplets might be in order to

obtain improved transmittance as a measurement for clarity, with higher transmittance indicating smaller droplet size and a finer emulsion or micro-emulsion as identified on page 12 of Applicant's disclosure which result provides an improvement of the uptake of cyclosporin into the system. This issue is simply not addressed within Woo as set out in Applicant's Claim 15.

> *15. A pharmaceutical composition comprising a micro emulsion preconcentrate yielding a droplet size in an emulsion of substantially less than 2000 A as measured by the light transmittance through a cell, and including a cyclosporin dissolved in an acetylated monoglyceride lipophilic solvent, and a surfactant.*

Woo may identify the use of a micro-emulsion concentrate requiring four essential components, namely cyclosporin as the active ingredient, a hydrophilic high molecular weight solvent (polyethylene glycol) as a co-surfactant, an oil component (a mixture of fatty acids as set out above), and a surfactant. There is no other teaching in Woo to arrive at Applicant's claim 15 above nor is there a discussion of the size of the droplets in an emulsion prepared from a pre-concentrate. In all the examples in Woo a mixture of oils is stated namely NIKKOL, MIGLYOL AND/OR MONOMULS as the oil component as defined in the disclosure of Woo. Clearly, though there is no discussion of only an acetylated mono-glycerides in combination with at least two surfactants as in Applicant's Claim 1 set out below.

> *1. A pharmaceutical composition comprising an emulsion preconcentrate including a cyclosporin dissolved in a solvent system comprising substantially fully acetylated monoglycerides having a minimum acetylation of 96%, a hydrophilic organic solvent and at least two surfactants.*

As set out at page 9 of Applicant's disclosure, Applicant has unexpectedly found surprisingly that the preferred surfactants have a synergistic action with other surfactants so that inclusion of a second surfactant as a co-surfactant can reduce the total amount of surfactant needed without loss of effectiveness in enabling dispersion to an emulsion or a micro-emulsion. Therefore, in Claim 1 Applicant has

included a limitation of at least two surfactants as supported in Applicant's disclosure which clearly identifies over either Woo or Kim again set out above.

Therefore, there is nothing within the teachings of either Kim or Woo alone or in combination which would result in Applicant's claims, and according to accepted Juris prudence provided with Applicant's preliminary amendment to which the Examiner is referred and which is incorporated by reference in it's entirety, it is clear that using Applicant's disclosure as a blueprint is entirely unacceptable in relying on a 20/20 hindsight reconstruction as set out in Hodosh v Block Drug Company, and other examples such as In re Rouffet to which the Examiner is referred to for further evaluation. There is nothing within the teachings of Kim or Woo, nor a combination of Kim and Woo that would motivate one of ordinary skill in the art to arrive at Applicant's independent claims 1 and 15 as set out above. There is no motivation in either reference to do so, and although these references may broadly be within the same discipline as stated by the Examiner, the alleged obviousness of the combination is now moot in view of Applicant's submissions, and full reconsideration is requested.

Claims 15, 17 to 19, now stand rejected under the judicially created doctrine of obviousness-type double patenting with regard to U.S. Patent No. 6,258,783. Applicant therefore files herewith a Terminal Disclaimer disclosing the portion of any patent issuing from the application beyond the expiry date of said patent. Reconsideration is therefore requested.

Attached hereto as **Exhibit A** is a marked-up version of the changes made to the claims by the present amendment. Exhibit A is entitled "EXHIBIT A - CLAIMS WITH MARKINGS TO SHOW CHANGES".

Attached hereto as **Exhibit B** is a clean set of all pending claims following entry of this amendment. Exhibit B is entitled: "EXHIBIT B - CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT". All

of the currently pending claims are consolidated in this list for the convenience of the Examiner.

Applicant encloses a cheque in the amount of **$1,350.00 USD** made payable to **"The Commissioner of Patents"** which consists of **$920.00 U.S** the fee required for filing the three month extension of time for a large entity; **$320.00 U.S.** to file the Notice of Appeal; and **$110.00 US** for filing the Terminal Disclaimer.

If there are any fees required with respect to the above-identified matters, Applicant authorizes the Commissioner to access Applicant Agent's Deposit Account No. 08-3255 and advise Applicant's Agent.

If the Examiner has any questions, she is respectfully requested to contact Applicants' Agent, Neil H. Hughes at (905) 771-6414 at her convenience.

Respectfully submitted,

Neil H. Hughes, P.Eng.
Registration No. 33,636
Agent for Applicant

NHH:mse
Enclosures

Amendment A
U.S. Application Serial No. 09/783,969
Group Art Unit 1614

EXHIBIT A

CLAIMS WITH MARKINGS TO SHOW CHANGES

Please amend the following claims.

15. A pharmaceutical composition comprising a micro emulsion preconcentrate [having] yielding a droplet size in an emulsion of substantially less than 2000 A as measured by the light transmittance through a cell, and including a cyclosporin dissolved in an acetylated monoglyceride lipophilic solvent, and a surfactant.

18. The composition of claim [1 or] 15 wherein the surfactant is selected from the group of a polyoxyethylene glycolated natural[,] or hydrogenated vegetable oil, polyoxyl 40 hydrogenated castor oil, and a polyoxyethylene-sorbitan-fatty ester.

19. The composition of claim 1 [or 15 comprising] wherein said at least two surfactants further comprise two surfactants, one of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil and the second of which is a polyoxyethylene-sorbitan-fatty acid ester.

Please add the following claims.

22. The composition of claim 1 wherein said at least two surfactants are selected from the group of a polyoxyethylene glycolated natural , hydrogenated vegetable oil, polyoxyl 40 hydrogenated castor oil, and a polyoxyethylene-sorbitan-fatty ester.

23. The composition of claim 15 wherein said surfactant further comprises two surfactants, one of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil and the second of which is a polyoxyethylene-sorbitan-fatty acid ester.